



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/00	A2	(11) International Publication Number: WO 99/45910 (43) International Publication Date: 16 September 1999 (16.09.99)									
(21) International Application Number: PCT/US99/05437 (22) International Filing Date: 12 March 1999 (12.03.99) (30) Priority Data: <table border="0"><tr><td>60/077,977</td><td>13 March 1998 (13.03.98)</td><td>US</td></tr><tr><td>09/065,012</td><td>23 April 1998 (23.04.98)</td><td>US</td></tr><tr><td>09/265,299</td><td>9 March 1999 (09.03.99)</td><td>US</td></tr></table> (71) Applicant: MUCOSAL THERAPEUTICS LLC [US/US]; Five Wynnwood Road, Wellesley, MA 02181 (US). (72) Inventors: SONIS, Stephen, T.; Eight Decatur Lane, Wayland, MA 01778 (US). FEY, Edward, G.; Apartment 3, 42 Commonwealth Avenue, Boston, MA 02115 (US). (74) Agent: PABST, Patrea, L.; Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).		60/077,977	13 March 1998 (13.03.98)	US	09/065,012	23 April 1998 (23.04.98)	US	09/265,299	9 March 1999 (09.03.99)	US	(81) Designated States: AU, BR, CA, IL, JP, MX, NZ, PL, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
60/077,977	13 March 1998 (13.03.98)	US									
09/065,012	23 April 1998 (23.04.98)	US									
09/265,299	9 March 1999 (09.03.99)	US									
(54) Title: METHODS AND COMPOSITIONS FOR TREATING AND PREVENTING MUCOSITIS (57) Abstract A method of reducing or inhibiting mucositis in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is disclosed.											

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakistan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

METHODS AND COMPOSITIONS FOR TREATING
AND PREVENTING MUCOSITIS

Background of the Invention

5 This invention relates to methods and compositions for treating
and preventing mucositis.

 Mucositis is the destruction of the oral mucosal epithelium,
which results in erythema, ulcerations and severe pain in the oral
cavity. Mucositis often arises as a complication of antineoplastic
10 therapy, such as cancer chemotherapy and/or radiation therapy. The
painful ulcerative lesions of mucositis can cause patients to restrict
their oral intake; as a result, they lose weight and suffer from fever
associated with dehydration. Severe mucositis can necessitate the de-
escalation of a planned chemo/radio-therapeutic dosing regimen to
15 prevent further damage to the oral mucosa.

 An even more serious consequence of mucositis is that the
lesions can act as sites of secondary infections and as portals of entry
for endogenous oral microorganisms. Mucositis is therefore a
significant risk factor for life-threatening systemic infection
20 (septicemia); the risk of systemic infection is exacerbated by
concomitant neutropenia, which is another complication associated
with chemotherapy. Patients with mucositis and neutropenia have a
relative risk of septicemia that is at least four times greater than that of
individuals without mucositis.

25 The overall frequency of mucositis varies; it is influenced by the
patient's diagnosis, age, and level of oral health, as well as the type,
dose, and frequency of drug or radiation administration.
Approximately 40% of all patients who receive cancer chemotherapy
suffer some degree of mucositis, and virtually 100% of patients treated

with radiation therapy for head and neck tumors develop mucositis. The frequency of severe mucositis in patients undergoing high risk protocols is over 60%. About 50% of individuals develop lesions severe enough to require modification of their cancer treatment and/or
5 parenteral analgesia.

The development of effective methods for treating and preventing mucositis has been hampered by a lack of understanding of the pathophysiology of this condition, and by the inconsistency in patient response to the medications currently in use.

10 Summary of the Invention

The invention features methods for treating and preventing mucositis. The invention is based, in part, on the recognition that mucositis is a complex biological process resulting from the cumulative and interactive effects of radiation and/or chemotherapy with epithelial
15 connective tissue and endothelium, pro-inflammatory cytokines, cellular elements within the mucosa and the local oral environment.

We hypothesize that mucositis represents a clinical outcome due to a complex interaction of local tissue (connective tissue, endothelium, epithelium) toxicity, the level of myelosuppression and
20 the oral environment. The local tissue components include an oral mucosa of rapidly renewing stratified squamous epithelium overlying a loose and richly vascular connective tissue base and appear to be responsive to changes in patients' bone marrow status and, particularly, the degree of granulocytopenia. The oral microbial flora, saliva and
25 functional trauma provide an indigenous environment which impacts on the frequency, severity and course of chemotherapy-associated stomatotoxicity.

It is quite likely that the initial oral tissue response to chemotherapy and radiation occurs at the endothelial and connective

tissue level. We believe that free radical formation leads to the disruption of fibronectin with subsequent activation of transcription factors, stimulation of pro-inflammatory cytokine production and tissue damage. A relationship between the presence of tumor necrosis factor-
5 alpha (TNF-) and IL-1 in serum correlates with the presence of non-hematologic toxicities. It is also likely that injury to endothelial cells occurs simultaneously. Concurrently, damage to the basal epithelial cells prevents their replication. It is unclear whether many of these cells undergo apoptosis or necrosis. An influx of inflammatory cells
10 expressing pro-inflammatory cytokines occurs during the breakdown of the mucosa and peaks just prior to the acme of mucositis. Bacterial colonization of the damaged epithelium occurs and is accelerated by the patient's myelosuppressed state. Typically the nadir follows a day or so after peak mucositis. Bacterial cell wall products from both gram
15 positive and gram negative organisms likely then penetrate the injured mucosa and further stimulate the release of damaging cytokines. Finally, the mucosa recovers, a process which takes about three weeks in the absence of secondary infection.

According to the invention, mucositis can be treated, or even
20 prevented, by the administration of inflammatory cytokine inhibitors, MMP inhibitors, and/or mast cell inhibitors. The combination of these inhibitors with an anti-inflammatory agent and/or an antimicrobial agent provides an even more effective regime for preventing and treating mucositis.

25 The invention features a method of reducing or inhibiting mucositis, in a patient suffering from mucositis or at risk for mucositis; the method includes administering to the patient a first therapeutic agent in an amount sufficient to inhibit mucositis, where the first therapeutic agent is an inflammatory cytokine inhibitor, a mast cell

inhibitor, an MMP inhibitor, or a combination of these inhibitors.

Preferred mast cell inhibitors include degranulation inhibitors, antihistamines, and serine protease inhibitors. A preferred MMP inhibitor is a tetracycline such as minocycline, which used by itself in
5 low doses is an effective mucositis agent that does not primarily act as an antibiotic. Other members of the tetracycline family can be used as well, e.g., chlortetracycline and oxytetracycline. An example of a mucositis that can be reduced or inhibited according to the invention is oral mucositis.

10 The invention also features a method of treating, inhibiting, or preventing mucositis in the human patient by administering to the patient first and second different therapeutic agents, the first agent being an NSAID (non-steroidal anti-inflammatory), an inflammatory cytokine inhibitor, or a mast cell inhibitor, and the second agent being
15 an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor, an NSAID, or an NO inhibitor. Preferably at least one of the agents is an NSAID, which is a COX-1 or COX-2 inhibitor; examples of COX-1 inhibitors are indomethacin and flurbiprofen. In other preferred embodiments, the first agent is an inflammatory cytokine
20 inhibitor selected from an IL-6 inhibitor, a TNF-alpha inhibitor, an IL-1 inhibitor, and an interferon-gamma inhibitor. A preferred combination is a TNF-alpha inhibitor combined with an MMP inhibitor such as a tetracycline, eg, minocycline. Exemplary NO inhibitors are aminoguanidine and guanidine. Another TNF-alpha inhibitor that can
25 be used is thalidomide. Mast cell inhibitors can be antihistamines, serine protease inhibitors, or degranulation inhibitors.

In other preferred methods, a third therapeutic agent, in an amount sufficient to inhibit infection, is administered as well; the third therapeutic agent includes an antimicrobial compound. Preferably, the

first, second, and third therapeutic agents are administered concurrently.

In another preferred method, the first therapeutic agent, in an amount sufficient to inhibit mucositis, and the third therapeutic agent, 5 in an amount sufficient to inhibit infection, are administered. Preferably, the first therapeutic agent and the third therapeutic agent are administered concurrently.

The mucositis being treated can be induced by antineoplastic therapy; for example, it can be induced by chemotherapy or by 10 radiation therapy. The patient treated with the methods and compositions of the invention can be a cancer patient preparing to undergo chemotherapy or radiation therapy, or a cancer patient currently undergoing chemotherapy or radiation therapy.

The invention further features a pharmaceutical composition for 15 treating oral mucositis that includes (a) a first therapeutic agent including an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor or a combination of these inhibitors; (b) a second therapeutic agent including an anti-inflammatory agent; and (c) a pharmaceutically acceptable carrier. The first and second therapeutic 20 agents are present in amounts sufficient to inhibit mucositis in a patient suffering from mucositis or at risk for mucositis. Preferably, the composition is formulated into a lozenge, a tablet, an oral rinse, an oral paste, or an oral gel. A preferred mast cell inhibitor is an antihistamine; preferred anti-inflammatory agents include non-steroidal 25 anti-inflammatory drugs and cyclooxygenase-2 inhibitors. Preferred MMP inhibitors include tetracyclines such as minocycline, tetracycline HCl, or doxycycline. Preferred compositions can also include an anti-ulcer agent, in an amount sufficient to inhibit gastric mucosal injury, and an antimicrobial agent, in an amount sufficient to inhibit infection.

Brief Description of the Drawing

Fig. 1 is a schematic representation illustrating the four phases of mucositis development and resolution.

Description of the Preferred Embodiments

5 The invention features methods and compositions for reducing and inhibiting mucositis that include administering inflammatory cytokine inhibitors and/or mast cell inhibitors.

 The invention is based, in part, on the development of a new mechanistic scheme for the physiological basis of mucositis.

10 According to this scheme, the development and resolution of mucositis occurs in four interrelated phases: (i) an inflammatory/vascular response; (ii) a degenerative connective tissue and/or epithelial phase; (iii) an ulcerative/bacteriological phase; and (iv) a healing phase. The four phases are illustrated in Fig. 1.

15 During phase 1, the inflammatory or vascular phase, the administration of chemotherapy effects the release of the cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-) from the epithelium. Alternatively, the administration of ionizing radiation causes the release of these cytokines from both the
20 epithelium and from the surrounding connective tissues.

 IL-1 induces an inflammatory response that results in increased sub-epithelial vascularity, with a consequent increase in the local levels of cytotoxic agents. Both IL-1 and TNF- cause local tissue damage, and thereby initiate and accelerate mucositis.

25 During phase 2, the degenerative epithelial phase, radiation and chemotherapeutic drugs affect the endothelium, the connective tissues and the dividing cells of the oral basal epithelium, resulting in reduced epithelial renewal, atrophy, and ulceration. The ulceration of the

surrounding tissue is exacerbated by functional trauma and by a flood of locally produced cytokines.

Phase 3, the ulcerative/bacterial phase, is the most symptomatic and perhaps the most complex. This phase generally occurs at the time
5 of the patient's maximum neutropenia. Phase 3 is characterized by the release of agents that stimulate cytokine production from bacteria on the lesions. Localized areas of full-thickness erosion develop, and a fibrous pseudomembrane sometimes grows over these areas. Secondary bacterial colonization of the lesions occurs, including
10 colonization with both gram positive and negative organisms; this stimulates cytokine release from the surrounding connective tissue, which further amplifies local tissue destruction.

During phase 4, the healing phase, epithelial proliferation and differentiation is renewed, the peripheral white blood cell count is
15 normalized, and the local microbial flora is re-established.

These four phases are interdependent; they are the consequence of a series of actions mediated by cytokines, the direct effect of the antineoplastic agents on the epithelium, connective tissue and endothelium, the oral bacterial flora, and the status of the patient's
20 bone marrow.

The invention is also based, in part, on the discovery that proliferation of mast cells plays a key role in the development of mucositis. Mast cells are granule-containing secretory cells which are present in mucosal and connective tissues, and which can migrate
25 within these tissues. The distribution of mast cells in tissues generally relates to the potential of mast cell-derived mediators to influence cells in the immediate environment. In the oral cavity, mast cells are preferentially distributed within the microvascular bed of the mucosa.

The granules of mast cells contain mediators that promote inflammation. Following degranulation, which can be triggered by a variety of stimuli, such as IgE, neuropeptides, trauma, and drugs, the mast cell mediators are deposited in large quantities in the extracellular environment. These mediators include histamine; the serine proteases chymase and tryptase; and cytokines, including TNF-. The mediators promote inflammation by exerting their effects on endothelial cells and other cell types. For example, the mediators may influence adhesion molecules and the behavior of the tissue, leading to ulceration.

Two of the most important of these mediators are histamine and TNF-. In the normal oral mucosa, these mediators are present only in the granules of mast cells, and are absent in other cells.

Mast cell-released histamine increases vascular permeability by effecting structural changes, such as endothelial contraction and intercellular gap formation. These changes result in increased local levels of chemotherapy-induced damage. In addition, histamine promotes leukocyte adhesion to endothelial cells via transient mobilization of the adhesion molecule, P-selectin, thereby causing inflammation.

Another important mediator released by mast cells is the cytokine TNF-. TNF- contributes to the inflammatory process by releasing histamine and by inducing endothelial expression of E-selectin, an adhesion molecule which is critically required for the rapid adhesion of neutrophils, T cells, monocytes, and other leukocytes to endothelial cells.

According to the invention, agents that inhibit the function of the mast cells or the action of the mediators released by mast cells can be used to treat and prevent mucositis. Mast cell inhibitors are chemical or biological agents that suppress or inhibit the function of

mast cells, or the mediators released by mast cells. For example, mast cell inhibitors can inhibit degranulation, thereby preventing the release of mediators into the extracellular space. Examples of mast cell degranulation inhibitors include picetannol, benzamidines, tenidap, 5 tiacrilast, disodium cromoglycate, lodoxamide ethyl, and lodoxamide tromethamine. Other agents that inhibit mediator release include staurosporine and CGP 41251.

Examples of mast cell mediator inhibitors include agents that block the release or secretion of histamine, such as FK-506 and 10 quercetin; antihistamines such as diphenhydramine; and theophylline.

Other mast cell inhibitors include serine protease inhibitors, such as -1-protease inhibitor; metalloprotease inhibitors; lisofylline; TNFR-FE (available from Immunex, Seattle, WA); benzamidine; amiloride; and bis-amidines such as pentamidine and bis(5-amidino-2- 15 benzimidazolyl)methane.

According to the invention, inflammatory cytokine inhibitors can also be used to treat and prevent mucositis. Inflammatory cytokine inhibitors are chemical or biological agents that suppress or inhibit inflammatory cytokines. Such inhibitors include pyridinyl imidazoles, 20 bicyclic imidazoles, oxpentifylline, thalidomide and gabexate mesilate.

Anti-inflammatory agents can be used in combination with inflammatory cytokine and/or mast cell inhibitors to treat and prevent mucositis according to the invention. Examples of anti-inflammatory agents that can be used in the present invention include the non- 25 steroidal anti-inflammatory drugs flurbiprofen, ibuprofen, sulindac sulfide, and diclofenac. When NSAID's are administered according to the invention, anti-ulcer agents such as ebrotidine can be administered, e.g., to help protect against gastric mucosal damage.

Other anti-inflammatory agents that can be used in the present invention include misoprostil; methylxanthine derivatives, such as caffeine, lisofylline, or pentoxifylline; benzydamine; naprosin; mediprin; and aspirin.

5 Another important class of anti-inflammatory agents includes cyclooxygenase (COX) inhibitors, particularly COX-2 inhibitors. COX-2, an inducible enzyme stimulated by growth factors, lipopolysaccharide, and cytokines during inflammation or cell injury, is responsible for the elevated production of prostaglandins during
10 inflammation. COX-2 inhibitors are especially useful where the invention is used to treat mucositis in cancer patients undergoing chemotherapy or radiation therapy, because of the gastrointestinal tolerability of these inhibitors. COX-2 inhibitors that can be used in the invention include celecoxib, nimesulide, meloxicam, piroxicam,
15 flosulide, etodolac, nabumetone, and 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4-fluoro)phenyl]pyrazole.

Other useful anti-inflammatory agents include dual cyclooxygenase/lipoxygenase inhibitors, such as 2-acetylthiophene-2-thiazolylhydrazone, and leukotriene formation inhibitors, such as
20 piriprost.

MMP inhibitors include both the antibacterial tetracyclines such as tetracycline HCl, minocycline and doxycycline, as well as non-antibacterial tetracyclines.

The presence of bacteria in the oral cavity leads to secondary
25 infection, serves as a source for systemic infection, and stimulates cytokine release, thereby amplifying tissue damage. According to the invention, the administration of anti-microbial agents in combination with the agents described above can result in an even more effective method for treating and preventing mucositis. Examples of

antimicrobial agents that can be used include agents with spectrum for gram positive and gram negative organisms. Specific drugs include tetracycline, amoxicillin, gentamicin, and chlorhexidine.

Other agents that can be used to treat or prevent mucositis
5 include the nuclear transcription factor kappa-B (NF- B) activation inhibitors capsaicin and resiniferatoxin.

Route and timing of administration

The route of administration is governed by the nature of the compound(s) used. For example, the compounds can be administered
10 in tablet or lozenge form, as an oral rinse, as a paste or gel, or by parenteral administration.

Since the compositions of the invention can help prevent mucositis, administration of the compositions should preferably precede the initial dose of antineoplastic therapy by at least 24 hours.
15 Daily treatment should continue during the course of antineoplastic treatment.

Dosage

The therapeutic agents described above can be used in the dose ranges currently used for these agents. For topical application, the
20 amount of drug to be administered will produce local tissue dose ranges equivalent to, or higher than, those achieved by parenteral administration. The following are illustrative examples of dose ranges.

Mast cell function inhibitors

The mast cell function inhibitor, picetannol, is preferably
25 administered to tissue or plasma levels of 0.1 g/ml to 5 g/ml; benzamidines are preferably administered to tissue or plasma levels of 0.5 to 1.0 M/l; tenidap is preferably administered to tissue or plasma levels of 1-200 M/l; and tiacrilast is administered in a 1% to 10% solution.

Mast cell mediator inhibitors

With respect to mediator inhibitors, lisofylline is preferably administered at 1 mg/kg to 10 mg/kg body weight, and TNFR-Fe (Immunex, Seattle, WA) is administered in 25 mg doses, twice weekly.

5

Anti-inflammatory agents

The anti-inflammatory agent, ibuprofen, is preferably administered at 50 mg to 800 mg per day, and flurbiprofen is preferably administered at 50 mg to 300 mg per day. The COX-2 inhibitor etodolac is preferably administered at 500 to 2000 mg per day; nabumetone is preferably administered at 500 to 2000 mg per day; meloxicam is preferably administered at 7.5 to 25 mg per day; piroxicam is preferably administered at 10 to 30 mg per day; and 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4-fluoro)phenyl]pyrazole is preferably administered at 1 to 10 mg/kg per day.

10

Anti-microbial agents

With respect to anti-microbial agents, tetracycline is preferably administered at 250 mg to 1000 mg per day, and chlorhexidine is preferably administered in a 0.1 to 5% solution, twice daily.

Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific examples are, therefore, to be construed as illustrative of the invention, and are not meant to limit the remainder of the disclosure in any way. Publications mentioned herein are hereby incorporated by reference.

20

MMP Inhibitors

Tetracyclines used as MMP inhibitors will be administered topically in dosages of .001 to 10 mg/mL, with a probable range of .01 to 1mg/mL, and an optimal range of .05 to .5 mg/mL.

Example 1: Prophylaxis and Treatment for Patients
Undergoing Myeloablative Chemotherapy and Total Body
Irradiation in Preparation for Bone Marrow Transplantation

For treatment according to the methods described herein,
5 patients are dosed with a topical application of mucositis medication as
a troche or lozenge, beginning the evening before the first dose of
chemotherapy. The lozenge contains therapeutic doses of an MMP
inhibitor such as minocycline and a nonsteroidal anti-inflammatory
agent such as flurbiprofen.

10 Beginning the day of chemotherapy and continuing for the
subsequent fourteen days, patients receive medication every 3 to 4
hours while awake. For patients unable to tolerate the lozenge because
of chemotherapy-induced nausea, a non-viscous liquid suspension is
available for dosing approximate every 2 hours while awake. Patients
15 using the suspension swish and gargle with the material to assure
exposure of the drug to the oropharynx. The fourteen-day dosing
period provides coverage through the first three phases of mucositis
development.

Example 2: Prophylaxis and Treatment for Patients

20 Undergoing Radiation Therapy for Tumors of the Head and
Neck

Patients being treated with radiation therapy for head and neck
cancers receive a total tumor dose of radiation of about 60 Gy, given in
divided doses over a 6-week to 8-week period. Early signs of
25 mucositis are noted at doses of around 10 Gy, and frank breakdown of
the mucosa is seen at around 25 Gy.

Beginning with the second week of this type of radiation
therapy, patients receive mucositis medication 2 hours prior to each
daily dose of radiation, which is typically given 5 days per week.

Subsequent mucositis medication is given 2 hours, 6 hours, and 12 hours following daily radiation. Since myelosuppression is not an issue for patients being radiated for head and neck cancers, the mucositis preparation includes mast cell inhibitors, cytokine inhibitors, and anti-inflammatory agents, but no anti-microbial agents. Patients do not receive mucositis medication on days on which they are not radiated. The protocol is followed until radiation dosing is completed.

Example 3: Prophylaxis and Treatment for Patients
Undergoing Chemotherapy Treatment for Treatment of
Colorectal Cancer

In treatments for colorectal cancer, patients typically receive multiple, monthly cycles of chemotherapy. Because of the use of specific anti-cancer drugs for treatment of this form of tumor, this group of patients is at particular risk for developing mucositis. Patients in this group begin dosing with mucositis medication two hours prior to chemotherapy administration. They continue taking mucositis medication every 4 hours, while awake, for at least the next 48 hours. The regimen is repeated for each dosing cycle. Generally, the formulation does not include an anti-microbial. However, for those patients demonstrating significant neutropenia, the formulation includes an anti-microbial, and treatment time is extended to ten days.

Other Uses

The methods and compositions of the present invention can be used to treat and prevent conditions such as lichen planus and graft-vs-host disease, which have similar biological mechanisms to that of mucositis.

Other embodiments are within the scope of the following claims.

We claim:

1. A method of treating, inhibiting, or preventing mucositis in a human patient, said method comprising administering to said patient first and second different therapeutic agents, wherein said first therapeutic agent is an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor; and said second therapeutic agent is an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor, an NSAID, or an NO inhibitor.
2. The method of claim 1, wherein at least one of said first and second agents is an NSAID which is a COX-1 or COX-2 inhibitor.
3. The method of claim 2, wherein said COX-1 inhibitor is indomethacin or flurbiprofen.
4. The method of claim 1, wherein the first agent is an inflammatory cytokine inhibitor selected from an IL-6 inhibitor, a TNF-alpha inhibitor, an IL-1 inhibitor, and an interferon-gamma inhibitor.
5. The method of claim 4 wherein the first agent is a TNF-alpha inhibitor and the second agent is an MMP inhibitor.
6. The method of claim 1 wherein said MMP inhibitor is a tetracycline.
7. The method of claim 6 wherein said tetracycline is minocycline.
8. The method of claim 6 wherein the first agent is an NSAID.
9. The method of claim 1 wherein the NO inhibitor is aminoguanidine or guanidine.
10. The method of claim 1 wherein the TNF-alpha inhibitor is thalidomide.

11. The method of claim 1 wherein the first agent is a mast cell inhibitor selected from an antihistamine, a serine protease inhibitor, and a degranulation inhibitor.

12. The method of claim 1 wherein the first and second agents are provided mixed together in a composition.

13. The method of claim 12, wherein the composition is a liquid adapted for use as an oral rinse.

14. The method of claim 12, wherein the composition is a solid adapted for oral ingestion.

15. A method of treating, inhibiting, or preventing mucositis in a human patient, said method comprising administering to said patient an effective amount of a therapeutic agent selected from an MMP inhibitor, an inflammatory cytokine inhibitor and a mast cell inhibitor.

16. The method of claim 15, wherein the mast cell inhibitor is a degranulation inhibitor.

17. The method of claim 15, wherein the mast cell inhibitor is an antihistamine.

18. The method of claim 15, wherein the mast cell inhibitor is a serine protease inhibitor.

19. The method of claim 15, wherein the MMP inhibitor is a tetracycline.

20. The method of claim 19, wherein the tetracycline is minocycline.

21. The method of claim 1, wherein said method further comprises administering to said patient a third therapeutic agent in an amount sufficient to inhibit infection, wherein said third therapeutic agent is an antimicrobial compound.

22. The method of claim 1, wherein said mucositis is induced by antineoplastic therapy.

23. The method of claim 22, wherein said mucositis is induced by chemotherapy.

24. The method of claim 22, wherein said mucositis is induced by radiation therapy.

25. The method of claim 22, wherein said patient is a cancer patient preparing to undergo chemotherapy or radiation therapy.

26. The method of claim 22, wherein said patient is a cancer patient currently undergoing chemotherapy or radiation therapy.

27. The method of claim 1, wherein said mucositis is oral mucositis.

28. A pharmaceutical composition for treating oral mucositis comprising

(a) a first therapeutic agent comprising an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor;

(b) a second, different therapeutic agent comprising an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor, an NSAID, or an NO inhibitor; and

(c) a pharmaceutically acceptable carrier, wherein said first and second therapeutic agents are present in amounts sufficient to inhibit mucositis in a patient suffering from mucositis or at risk for mucositis.

29. The pharmaceutical composition of claim 28, wherein said composition is formulated into a lozenge, a tablet, an oral rinse, an oral paste, or an oral gel.

30. The pharmaceutical composition of claim 28, wherein said mast cell inhibitor is an antihistamine.

31. The pharmaceutical composition of claim 28, wherein said anti-inflammatory agent is an NSAID.

32. The pharmaceutical composition of claim 31, wherein said composition further comprises an anti-ulcer agent in an amount sufficient to inhibit gastric mucosal injury.

33. The pharmaceutical composition of claim 28, wherein said anti-inflammatory agent is a cyclooxygenase-2 inhibitor.

34. The pharmaceutical composition of claim 28, wherein said composition further comprises an antimicrobial agent in an amount sufficient to inhibit infection.

FIG. 1

